

Evaluation of an Oxygen-Diffusion Dressing for Accelerated Healing of Donor-Site Wounds

Kimberly F. Laiet, MD, David Baer, PhD, Michelle L. Leas, RN,
Evan M. Renz, MD, Leopoldo C. Cancio, MD

Accelerating the healing process and reducing pain during healing are beneficial for the following reasons: faster return to work, lower risk of wound infection, improved quality of life, and possibly reduced need for analgesia. This clinical study assessed the effectiveness of a new oxygen-diffusion dressing (OxyBand; Oxyband Technologies, St. Louis, MO) compared with standard Xeroform gauze dressings (Convidien, Mansfield, MA), in the care of skin-graft donor sites in burn patients. Time to healing was the primary endpoint, and pain scores and cosmetic outcome were also assessed. This was a prospective, randomized, controlled study of burn patients undergoing harvesting of two donor sites. Patients were followed at predetermined time points for 30 to 45 days to determine the time to reepithelialization, cosmetic appearance, and pain. Subjects were adult burn patients with less than 30% TBSA burns admitted to the burn center, who required excision and grafting. Twenty patients were enrolled, of whom 17 completed the study. Average age was 35 years. Average burn size was 9.2% TBSA. Patients underwent harvesting of split-thickness skin grafts with one donor wound dressed with OxyBand and the other dressed in Xeroform gauze. Wounds were inspected and photographed on postoperative days 4 and 8, and then every 2 days until the donor wounds were healed. Pain scores at each site were also collected at these visits (rated by patients on a scale from 0 to 10). Mean time to wound healing for OxyBand was 9.3 ± 1.7 days; for Xeroform, 12.4 ± 2.7 days ($P < .001$). Pain scores were lower ($P < .01$) at the OxyBand site compared with the Xeroform site at all time points during postoperative days 4 to 12. There was no difference in the cosmetic outcome of the wounds at 30 to 45 days postoperatively. This study revealed a decrease in the time to healing and in pain at donor sites dressed with an oxygen-diffusion dressing. (J Burn Care Res 2014;35:214–218)

Donor sites generated in conjunction with split-thickness skin grafting during burn care have been

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Address correspondence to Leopoldo C. Cancio, MD, U.S. Army Institute of Surgical Research, 3698 Chambers Pass, Fort Sam Houston, TX 78234-6315.

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treated with a variety of topical agents, such as fine-mesh gauze, scarlet-red gauze, Xeroform gauze, and other dressings. Slow healing times, cellulitis, and pain are perennial problems in the care of these wounds. An ideal donor-site dressing would provide an optimal environment for reepithelialization while minimizing pain, preventing infection, and promoting the best cosmetic outcome possible.

Extensive investigation has been performed on the effects of oxygen on wound healing. Oxygen has been found to be important in angiogenesis, collagen synthesis, wound contraction, epithelialization, and prevention of infection,^{1–4} all of which are necessary for tissue repair and wound healing. Animal and laboratory studies have shown that decreased oxygen levels in the wound result in impaired fibroblast proliferation and collagen deposition, reduced tensile strength, higher rates of infection, and reduced mobility of specific cells.^{3–5} In a rabbit model,

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wounds were treated with 100% topical oxygen supplied continuously, and full-thickness punch biopsies were evaluated for epithelialization. The topical oxygen treatment group demonstrated significantly greater healing response compared with controls, with a near doubling in the epithelial wound coverage in the treatment group.⁶ Another animal study, using rats, examined the size of wounds over time treated with an oxygen-generating dressing versus a control dressing. The rats treated with oxygen-generating dressing had a significantly shorter time to closure of their wounds, compared with a similar occlusive dressing without oxygen.⁷ Hyperbaric oxygen therapy is thought to improve healing of chronic wounds in humans,⁸ but requires visits to facilities with trained personnel and is limited by oxygen toxicity issues. Compared with hyperbaric oxygen therapy, the benefits of topical oxygen would include lower cost, lack of systemic oxygen toxicity, and the ability to receive treatment at home.^{9,10}

OxyBand is a U.S. Food and Drug Administration-approved (K043063) wound dressing for delivery of oxygen into the wound. This multilayer dressing comes prefilled with high levels of oxygen between the layers. The top layer is a barrier film that holds the oxygen over the wound, whereas the bottom layer is a high-transfer-rate film, attached to the wound. The barrier layer holds the oxygen in the vicinity of the wound, whereas the permeable or porous layer allows the oxygen to diffuse into the wound. The dressing acts like an oxygen reservoir. It is intended to allow the wound to use as much oxygen as needed, and to supply oxygen on demand as the wound consumes oxygen from the wound fluid. The dressing tends not to adhere to the donor site itself, but rather is designed to adhere to its periphery by means of an adhesive portion.

Xeroform gauze (3% bismuth tribromophenate and United States Pharmacopeia petrolatum on fine-mesh gauze) has been the preferred donor-site dressing used at this burn center for several years. In this clinical study, we compared the OxyBand dressing with the Xeroform dressing with respect to donor-site healing time. Secondary endpoints included pain and cosmesis.

MATERIALS AND METHODS

This study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board, and in accordance with the approved protocol.

We performed a single-center, prospective, randomized, controlled, open-label study to compare

the effectiveness of OxyBand and Xeroform dressings used as dressings for autogenous skin donor sites in burn patients. Informed consent was obtained from each patient enrolled in the study. Subjects were adult burn patients with less than 30% TBSA thermal injuries admitted to the U.S. Army Institute of Surgical Research Burn Center, who required surgical management of their wounds. Exclusion criteria included significant comorbid medical conditions that could impair healing (such as diabetes or peripheral vascular disease), patients diagnosed with burn wound cellulitis preoperatively, and critically ill patients on mechanical ventilation who would be unable to provide consent for the study or participate in the postoperative questionnaires.

Patients were scheduled for excision and grafting of burn wounds, with a requirement of at least two donor sites. Epinephrine in lactated Ringer's solution at a concentration of 1:10⁶ was injected subcutaneously to prepare both donor sites for harvesting for all patients but one. Donor sites were harvested using a Zimmer dermatome set at 0.0010 inch depth to ensure uniform thickness of the harvested skin. Hemostasis was achieved by brief application of gauze sponges dipped in epinephrine in lactated Ringer's solution at a concentration of 1:200,000. The wounds were then treated with either the OxyBand dressing (Figure 1) or Xeroform gauze. A randomization table was used to determine which donor site was treated with which dressing.

Postoperatively, the donor wounds and dressings were inspected daily until postoperative day 4, then every 2 days until both wounds were healed. The OxyBand dressings were changed on postoperative days 4 and 8, and then every 2 days until healed. In addition, the OxyBand dressings were changed more frequently if the adhesive edges became nonadherent, or in the presence of an excessive amount of exudate (as may occur in the immediate postoperative period). Xeroform dressings were not changed. Photographs were taken of the wounds at these time points, and the patients were asked to rate their pain (on a scale of 0–10) at each donor site on these visits. Pain ratings were performed at rest, before performance of dressing changes. Patients whose donor sites were not healed by the time of discharge from the hospital were given instructions to return to the burn clinic every 2 days for donor-wound assessments until both wounds were healed.

"Healed" was defined as the day on which, in the opinion of one of the staff burn surgeons, 90% or more of the wound surface was reepithelialized. The decision whether a wound was healed or not was made purely on clinical appearance. Between days



Figure 1. Typical appearance of OxyBand dressing on a donor site.

30 to 45 after surgery, the patient's donor sites were evaluated for cosmesis. Digital photos were evaluated later by a burn surgeon blinded to the dressings and not associated with the study, according to the scar-assessment scale developed by Yeong et al.¹¹

The design of the OxyBand dressing incorporates a circular pattern on the surface of the dressing, which interfaces with the wound. When considering the dressing for a clinical trial on human donor-site wounds, concern was raised about the potential for wounds to heal with this circular pattern, as it would leave the patient with an inconsistent scar or a pseudo-tattoo. To further investigate this concern, a separate animal study was conducted before enrollment of patients in the clinical trial described in this article. The study animal received six wounds, identical to human donor-site wounds in depth and size, five of which were dressed with OxyBand, and one with Xeroform. At 2 weeks after operation, a faint circular pattern was observed in two of the OxyBand wounds. This pattern disappeared and, at 30 days, all wounds were evenly healed with no discernible pattern.

Because there was a temporary pattern observed in some of the study pigs' wounds during the healing process, the human clinical study paused for a safety analysis after the first six patients were enrolled. The first six patients were followed up for 30 to 45 days postoperatively, and their wound photographs were interpreted by a burn surgeon not affiliated to the study. The results were discussed by a panel before proceeding with study. As there was no significant difference noted in the 30- to 45-day cosmetic outcome of the OxyBand versus the control wounds, the study continued to completion.

A power analysis conducted by our statistician concluded that 17 patients, providing 34 matched donor sites, would be required to demonstrate a difference

in healing time with a confidence level of 95%. Data were analyzed using the Statistical Analytical Software. Continuous and score variables were compared via Wilcoxon test for nonparametric data. All tests for significance were two-tailed with $\alpha = .05$.

RESULTS

A total of 20 patients were enrolled, of whom 17 completed the study. Of the three who did not complete the study, one enrolled patient required only one donor wound in the operating room. Another patient was enrolled but was not studied because surgery was deemed unnecessary on repeat examination. A third patient did not return for study visits and was lost to follow-up. Eight military and 12 civilian patients were enrolled, with three women and 17 men. Mean age was 35.0 (range, 20–49) years. Mean burn size was 9.2% TBSA (range, 2–24%).

OxyBand donor sites healed in an average of 9.4 ± 1.7 days (range, 6–12 days). Xeroform sites healed in an average of 12.4 ± 2.7 days (range, 8–20 days) ($P < .01$). There were no wound infections in either group. Two patients were found to have blisters at their donor sites at their final 30- to 45-day visit; the blisters were present at both OxyBand and Xeroform sites. No other unanticipated events occurred.

Study patients were asked to rate their pain on a scale of no pain (0) to maximum pain (10) at each donor site at set points in the study. These assessments were made at rest, before the performance of dressing inspections or changes. On postoperative day 4, pain at the OxyBand site averaged 0.6, whereas Xeroform sites were rated an average of 1.6 ($P < .05$). Pain diminished by postoperative day 8, but was still significantly less at the OxyBand site (0.4) than at the Xeroform site (1.4; $P < .05$). By postoperative days 10 and 12, few patients reported any pain. There continued to be a statistically significant difference between the two groups, however. At postoperative 10, the average pain rated at OxyBand sites was 0.3 compared with 0.8 at the Xeroform site ($P < .05$). On postoperative 12, pain score of OxyBand wound averaged 0.2, with Xeroform wound receiving an average 0.5 rating ($P < .05$).

At the conclusion of the study, photographs of the patients' donor wounds (from days 30–45) were analyzed by two surgeons not associated with the study. Of the 17 patients, there were 13 sets of photos for final evaluation of cosmetic outcome. Three patients' photos were inaccessible because of technical difficulties. Of the 13 evaluable sets of photos, four patients' wounds (OxyBand vs Xeroform) were without significant difference in cosmetic

appearance, four patients' OxyBand wounds were judged to have better cosmetic outcome, and five patients' Xeroform wounds were deemed to have better cosmetic appearance.

Nursing time was not measured in this study. Each patient visit required 30 to 45 minutes of hands-on time by the research nurse, or up to 60 minutes if photographs were taken. The time required to perform an OxyBand dressing change was on the order of 2 minutes.

DISCUSSION

The harvesting of donor sites during split-thickness skin-grafting procedures creates a new wound. Care of such wounds involves techniques to promote rapid reepithelialization. The longer the wound remains open, the higher the risk of infection. Dressings that optimize the donor-site healing allow for reharvesting of donor sites more rapidly, which can be life-saving for patients with large burn surface area involvement. Dressings such as Xeroform have been used for many years as donor-site dressings because of their availability, low cost, and relative ease of application. This study prospectively compared a new product, OxyBand, with our control donor-site dressing, Xeroform. Healing time, as well as perceived pain and cosmetic outcome, were assessed.

We found a statistically significant decrease in the healing time of donor-site wounds dressed with the OxyBand dressing compared with the Xeroform-dressed wounds. Not one of our subjects had a donor wound dressed with Xeroform heal faster than the study wound, although some subjects' wounds were found to be healed on the same day.

Our results also demonstrated that the OxyBand dressing was associated with less pain at each post-operative data-collection point. Subjects' comments about the dressings were recorded at their final 30- to 45-day visit, and every patient who made a comment had a positive remark about the comfort of OxyBand dressings. No such remarks were made about the comparison dressing. The OxyBand dressing keeps the wound occluded and moist during the healing process. In contrast, Xeroform is left exposed to the air in order to dry. It eventually hardens before it separates from the wound as it is reepithelialized. The nonadherent characteristic of the OxyBand dressing (with regard to the wound) may explain the decreased pain reported at the wound site by subjects. Whether topical oxygen also modulates the pain response is unknown. Further studies should be done to look more closely at the relationship between oxygen-diffusion dressings and pain.

The type of dressing used did not have an impact on the final cosmetic outcome of the wound. There was no pattern formation in the final OxyBand wounds at 30 to 45 days, and cosmetic appearance was judged to be similar to the control Xeroform wounds by independent surgeons familiar with burn wounds.

A border of approximately 2 cm on all sides of the wound is required for the OxyBand dressing to adhere, which must be taken into consideration. At the time of this clinical study, only one size of the dressing was available. This, of course, is a limitation in comparison with Xeroform, which can be trimmed to fit or pieced together to fit virtually any size wound. Although a variety of sizes and configurations of the OxyBand dressing could be manufactured, it still likely will require some uninjured skin around the margins to allow the dressing to adhere.

Xeroform dressing has been widely available for many years and is inexpensive. The commercial cost of OxyBand dressings is not yet known, but will almost certainly cost more than Xeroform gauze. The decreased levels of pain reported by patients, and possibly the decreased requirements for pain medication as a result, may help offset the price of the OxyBand dressing. It is also difficult to place a price on the value of time to healing. For a patient with a large percent body surface area full-thickness burn, speeding healing by a few days would allow more rapid coverage of the excised wounds with autologous tissue. This may prevent an infection or reduce the amount of temporary closures (allograft, Integra, or other products) before final closure is achieved.

A limitation of the study involved being able to determine the day of healing of each wound. This issue was multifactorial. In a few instances, patients were late for follow-up visits, so the true day of healing may have been the day prior. Also, the OxyBand dressing was not removed every day to inspect the wound. To maximize the benefit the wound would receive from being in an oxygen-saturated environment, the decision was made to initially only remove the dressing on postoperative days 4 and 8. The frequency of dressing changes was then increased to every 2 days in an attempt to more closely capture the day of healing, as our experience has been that most donor wounds are healed approximately 10 to 14 days after skin harvest. Perhaps if the dressing was changed daily, we may have more accurately identified the day of healing. This idea was rejected, however, as patient compliance with the follow-up visit schedule may have been reduced. Another limitation is the unblinded nature of this study.

It is not possible, based on the results of this study alone, to conclude that the advantages of the OxyBand dressing were solely because of the oxygen content; other characteristics of the dressing may have contributed to our observations. For example, the OxyBand dressing provides a more moist environment; this may contribute to wound healing. In addition, the OxyBand dressing does not adhere as much to the wound bed, which may contribute to reduced pain. A placebo dressing containing air rather than oxygen was not available for this study. Also, we did not measure oxygen levels at the wound surface. These factors represent limitations in the design of our study.

For skin donor sites in burn patients, we conclude that use of an oxygen-diffusion dressing was associated with, on average, a 3-day decrease in wound healing time as well as a decrease in postoperative pain.

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REFERENCES

1. Hopf HW, Gibson JJ, Angeles AP, et al. Hyperoxia and angiogenesis. *Wound Repair Regen* 2005;13:558–64.
2. Whitney JD. Physiological effects of tissue oxygenation on wounds. *Heart Lung*. 1989; 18(5):466–74.
3. Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. *Am J Surg* 2003;186:259–63.
4. Rahat MA, Marom B, Bitterman H, Weiss-Cerem L, Kinarty A, Lahat N. Hypoxia reduces the output of matrix metalloproteinase-9 (MMP-9) in monocytes by inhibiting its secretion and elevating membranal association. *J Leukoc Biol* 2006;79:706–18.
5. Tandara AA, Mustoe TA. Oxygen in wound healing—more than a nutrient. *World J Surg*. 2004;28(3):294–300.
6. Said HK, Hijjawi J, Roy N, Mogford J, Mustoe T. Transdermal sustained-delivery oxygen improves epithelial healing in a rabbit ear model. *Arch Surg*. 2005;140(10):998–1004.
7. Wright TE, Payne WG, Ladizinsky D, et al. The effects of an oxygen-generating dressing on tissue infection and wound healing. *J Appl Res Fall*. 2003;3(4):363–70.
8. Thackham JA, McElwain DL, Long RJ. The use of hyperbaric oxygen therapy to treat chronic wounds. *Wound Repair Regen*. 2008;16(3):321–30.
9. Kalliainen LK, Gordillo GM, Schlinger R, Sen CK. Topical oxygen as an adjunct to wound healing: a clinical case series. *Pathophysiology* 2003;9:81–7.
10. Feldmeier JJ, Hopf HW, Warriner RA 3rd, Fife CE, Gesell LB, Bennett M. Undersea Hyperbaric Medicine Society (UHMS) position statement: topical oxygen for chronic wounds. *Undersea Hyperb Med*. 2005;32(3):157–68.
11. Yeong EK, Mann R, Engrav LH, et al. Improved burn scar assessment with the use of a new scar-rating scale. *J Burn Care Rehab*. 1997;18(4):353–5.